SUPPLEMENTARY MATERIALS

Literature Review of Trial Level Risk Factors of Poor Accrual

Given the large number of studies that have addressed accrual in cancer trials, we conducted two pragmatic and more targeted searches that were limited to either (a) previously published reviews, or (b) studies within a cancer cooperative group or network setting. The pre-specified search terms were: clinical trial[MeSH Terms] AND cancer[MeSH Terms] AND (particip* OR accru* OR feasib* OR enroll* OR recruit*). We additionally selected the review filter on PubMed for (a) whereas for (b) we included an additional search term (cooperative OR network).

In total we identified (a) 81 and (b) 79 previously published papers that met our initial inclusion criteria. We reviewed the titles and abstracts of these studies to identify a subset of (a) 15 and (b) 23 that appeared relevant to our study question. We excluded studies that evaluated accrual exclusively in pediatric or adolescent settings, but included studies that reported quantitative, qualitative, or commentary on accrual challenges as our goal was to develop as complete a conceptual model as possible and we did not wish to exclude from consideration putative factors that currently lacked empirical evidence. Details regarding the reasons for inclusion or exclusion of these studies in our final analysis and the key findings from each study that was included are summarized in Supplementary Table 1.

Supplementary Table 1. Summary of previously published studies in cooperative group or network settings that were included in the first-level review (n=23).

	Reference	Included in final review?	Rationale for exclusion, or study setting if included	Key findings
1	(1)	No	Only evaluated physician-related factors that are not likely to differ across trials (e.g. physician age or specialty); no trial-level variation	
2	(2)	No	Recommendations from ASCO-Trial Accrual Symposium on strategies to improve accrual; did not report specific barriers or challenges	
3	(3)	No	Physician opinion regarding toxicity risk in Phase I studies only	
4	(4)	Yes	Survey of 94 NSABP principal investigators asking why they were not entering eligible patients in a trial to compare segmental mastectomy and postoperative radiation, or segmental mastectomy alone, with total mastectomy	▪ Concern that the doctor-patient relationship would be affected by a randomized clinical trial ▪ Difficulty with informed consent ▪ Dislike of open discussions involving uncertainty
5	(5)	Yes	A survey of study chairs and lead statisticians of 248 NCI-sponsored trials.	▪ Concluded that accrual *success* was attributable to: perceived clinical relevance of the study question, lack of competing trials, and a protocol designed to parallel normal practice. However, trial chairs and statisticians did not identify consistent factors to explain accrual difficulties ▪ Also reported that a CTCG's accrual experience in a particular disease, disease stage, or intervention was viewed as the strongest influence on accrual predictions
6	(6)	Yes	Accrual experience of National Cancer Institute Cooperative Group phase III trials activated from 2000 to 2007	▪ Better accrual in trials evaluating a new investigational agent ▪ Poorer accrual in trials with randomized design
7	(7)	No	Survey of sites enrolling patients onto cooperative group trials that address site-specific information only (no trial-level variation)	
8	(8)	Yes	Analyzed accrual to selected phase II and phase III cooperative group non-small-cell lung cancer (NSCLC) trials	▪ Accrual to multimodality trials was poorer than single modality trials ▪ Poorer accrual to trials involving radiation or surgery alone

				versus chemotherapy ▪ Trend towards better accrual in advanced NSCLC versus early stage disease.
9	(9); (10)	No	Only evaluated patient-related factors that are not likely to differ across trials; no trial-level variation	
10	(11)	No	Did not evaluate challenges to patient accrual	
11	(12)	No	Did not evaluate challenges to patient accrual	
12	(13)	Yes	Survey sent to Ontario-based cancer centers who treated women with breast cancer and cooperative pharmaceutical companies identified by experts in breast cancer field	▪ Poorer accrual in trials with placebo, non-metastatic versus metastatic setting, and shorter enrollment window from incident event (e.g. diagnosis, surgery) to study entry.
13	(14)	Yes	Summary of recommendations from a 1-day symposium that addressed the current challenges of NSCLC clinical trial accrual, hosted by the Coalition of Cancer Cooperative Groups	▪ Compelling research question relevant to current clinical practice ▪ Financial reimbursement that covers the cost of implementing the study and provision of adequate and trained resource support ▪ Simple study design ▪ All treatment arms viewed as acceptable ▪ Short time from letter of intent submission to trial activation
14	(15)	Yes	Analysis of patient eligibility for and reasons for non-entry into phase I trials in a single hospital setting	▪ Patients often ineligible due to poor performance status, too many prior treatments, or rapid disease progression ▪ Primary reasons for non-entry were patient refusal, other treatment recommended first, and lack of available trials
15	(16)	No	Discussion of biopsychosocial human processes that may affect accrual in surgical oncology trials	
16	(17)	Yes		▪ Older age is barrier to clinical trial enrollment
17	(18)	Yes	Evaluation of state mandates for payer coverage of clinical	▪ Overall state coverage policies ensuring reimbursement for routine medical care costs were not associated with a significant increase in trial enrollment of patients with private insurance ▪ Subgroup analysis of phase II trials showed enactment of coverage policies was associated with significant increase in enrollment compared to states without coverage policies.
18	(19)	No	Single institution study	
19	(20)	Yes	Why older patient don’t enroll	▪ Protocol exclusion criteria and functional status limitations

				were associated with lower elderly participation
20	(21)	No	Survey of attitudes of American adults without cancer toward participation in cancer clinical trials; did not evaluate any differential factors of attitudes towards enrollment	
21	(22)	Yes	Study of physicians reluctance for referring breast cancer patients to clinical trials.	▪ Older patients and those with worse prognosis were less likely to be referred for clinical trials ▪ Patients who delayed treatment decisions were more likely to participate [note: biased result] ▪ Oncologists less likely to refer patients if entry criteria were more stringent or onerous
22	(23)	No	Did not evaluate challenges to patient accrual	
23	(24)	No	Did not evaluate challenges to patient accrual	
	(25)	Yes	Evaluated range of factors within a subset of 82 phase III trials opened by five CTCGs between August 1991 and March 2004	▪ Therapeutic trials more likely to achieve sufficient accrual than nontherapeutic trials ▪ Trials studying chemotherapy or immunotherapy more likely to achieve sufficient accrual than those studying radiation therapy or surgical procedure ▪ Trials with a placebo arm less likely to achieve sufficient accrual

Supplementary Table 2. Summary of previously published systematic reviews included in the first-level review (n=15).

	PMID	Included in final review?	Rationale for exclusion, or study setting if included	Key findings
1	(2)	N/A	Included in table above	
2	(26)	No	Did not evaluate challenges to patient accrual	
3	(27)	No	Did not evaluate challenges to patient accrual	
4	(28)	Yes	Reviews the current literature addressing the obstacles to accrual excluding those related to protocol design	▪ Key physician-related factors associated with accrual difficulty were: concerns about treatment arms, earlier stage disease, time commitment for trial, preference for a particular treatment, perception of importance of clinical question, entry requirements. ▪ Key patient-related factors associated with accrual difficulty were: dislike of randomization, concerns about toxicity, desire to choose another treatment, stringency of eligibility criteria, inconvenience, placebo arm in trial.
5	(29)	No	Findings were highly specific to colorectal cancer screening studies and not generalizable	
6	(30)	Yes	Review of "what is known about the factors that influence cancer clinical trial decision making"	▪ Existence of alternative treatment options, worse benefit to risk profiles, greater time and travel requirements, and worse general health characteristics were associated with lower likelihood of participating in clinical trial.
7	(31)	No	Did not evaluate challenges to patient accrual	
8	(14)	N/A	Included in table above	
9	(32)	Yes	Systematic review. Objective was to investigate the barriers, modifiers, and benefits involved in participating in randomized controlled trials of cancer therapies as perceived by health care providers and patients.	▪ Patient-related factors associated with declining trial enrollment were: treatment preference (either for or against a specific treatment arm) and greater uncertainty (of side-effects or outcomes) ▪ Health system-related factors associated with barriers to trial enrollment were: greater time (extra work, discussions with patients, ethics submissions), greater resources requirements, lack of trial having a good scientific rationale, trial not designed to be in line with standard practice, or protocol not easy to comply with, and lack of trial relevance.
10	(33)	Yes	Meta-analysis and systematic review of patient-reported barriers to participation in	▪ Patient reported barriers to participations included: concerns with the trial setting; dislike of randomization; discomfort with

			clinical trials in cancer	research process; complexity and stringency of the protocol; presence of a placebo or no-treatment group; potential side-effects; being unaware of trial opportunities; idea that clinical trials are not appropriate for serious diseases; fear that trial involvement would have a negative effect on the relationship with their physician; and their physician's attitudes towards the trial.
11	(17)	N/A	Included in table above	
12	(34)	Yes	Review and commentary on reasons for non-participation in clinical trials, with specific reference to the field of cancer research.	▪ Trial-level factors associated with poor accrual were increased burdens of trial participation for the individual (demands on time, travel difficulties, duration of trial), and objection to randomization.
13	(35)	No	Did not evaluate challenges to patient accrual	
14	(36)	No	Discussion of patient participation in cancer chemoprevention trials. Did not report on specific barriers to accrual. [Re-CHECK this one]	
15	(37)	Yes	Review of literature on accrual to cancer therapy trials	▪ Trial-level factors associated with poorer accrual included: more numerous and stricter eligibility criteria, 'no treatment' arms and treatment arms of unequal attractiveness

Identification and Classification of Clinical Condition(s) Studied in Prediction Model

Supplementary Table 3. Total number of clinical trials studying each of the clinical conditions evaluated by one of the NCTN-supported trials included in our main analyses.

Clinical Condition	Text Search Terms	Number Trials Sponsored by NCTN	Number Trials Not Sponsored by NCTN
Anal	anal, anus	4	41
Bladder & Uretheral	bladder, urothe, ureth, urinary	23	167
Bile	bile, biliary	5	60
Brain & Central Nervous System	brain, central nervous system, gliobastoma, glioma, cns	37	436
Breast	breast	104	1184
Cervical	cervic, cervix, fallopian	54	233
Colon & Rectal	colon, colorectal, rectal, rectum	53	591
Endometrial	endometrial, uterine, uterus	68	255
Esophageal	esophageal	24	183
Kidney	kidney, renal	31	315
Larynx	larynx, laryngeal	4	38
Leukemia	leukemia, hemato	66	950
Liver	liver, hepatic, hepato	16	334
Lung & Bronchus	lung, bronch	94	995
Hodgkin's Lymphoma	Hodgkin [but NOT any terms for Non-Hodgkin's lymphoma, see below]	10	102
Non-Hodgkin's Lymphoma	non-hodgkin, nonhodgkin, mantle cell, t-cell lymphoma, t cell lymphoma, b-cell lymphoma, b cell lymphoma, burkitt, lymphocytic lymphoma	55	641
Melanoma	melanoma	23	347
Myeloma	myeloma, plasmacytoma	20	330
Oral	oral, mouth, pharyn, salivary gland	16	250
Ovary	ovar	57	356
Pancreas	pancrea	21	327
Prostate	prostate, prostatic	54	675
Stomach	gastric, stomach	15	191
Testis	testi	3	21
Vulvar	vulva	5	13
Lymphoma, NOS*	lymphoma, hemato	7	190
Sarcoma	sarcoma	45	278
Neuroblastoma	neuroblastoma	2	52
Mesothelioma	mesothelioma	11	44
Head & Neck, NOS	head, neck, h&n	40	318
Thymoma	thymoma, thymic	1	14
Penile	penile	1	4
Merkel	merkel	1	3
Trophoblastic	trophoblast	5	6
Neuroendocrine	neuroendocrine, islet cell, net	2	53
Gastrointestinal Stromal Tumor	gastrointestinal stromal, gist	3	48

Waldenstrom	waldenstrom, macroglobulinemia	3	21
Non-specific cancer condition	[includes cancers of 'unknown primary' and symptom management or supportive care in non-specific cancer conditions]	33	250

*Not including those identified as Hodgkins or Non-Hodgkins Lymphoma.

We verified the algorithm by manually evaluating its performance in a random sample of 100 trials drawn from the complete portfolio of trials on ClinicalTrials.gov (4 were NCTN-sponsored). The initial algorithm correctly classified all trials except 4 of 7 in lymphoma because we did not properly exclude non-Hodgkin's lymphoma from the Hodgkin's lymphoma classification. We therefore modified our algorithm and verified that it correctly classified conditions in an additional sample of 25 trials that included any 'lymphoma' term.

Clinical categories are not mutually exclusive (i.e. overlap is possible within trials) and are only collectively exhaustive of NCTN-sponsored trials. In other words, certain clinical conditions are not represented (e.g. basal cell carcinomas) if there were no late-phase NCTN-sponsored trials in the condition included in our final dataset.

Accounting for Misclassified Number of Competing Trials Launched Prior to 2007

Overview

The number of trials launched prior to September 2007 is measured with error because registration was not uniformly required; however, registration was required after September 27, 2007 for all new trials (and after December 31, 2007 for all ongoing trials). We therefore used the sample of trials started after 2007 as a validated subset in which the total number of trials and level of competition was measured without error. We recalibrated the measure of competition for trials started before September 2007 using missing data techniques (i.e. multiple imputation), following the approaches described in detail elsewhere (38-40).

Comparing Competition as Measured Before and After September 2007

We evaluated the total number of late phase cancer clinical trials registered on ClinicalTrials.gov in each year after 2007. We found relatively consistent total number of trials over time: 1469, 1443, 1348, and 1429 launched in 2008, 2009, 2010 and 2011, respectively. We therefore assumed that there were approximately as many late phase cancer trials launched in each year prior to 2008 as well.

We next assumed that trials not registered on ClinicalTrials.gov were missing at random for the purposes of these analyses conditional on the amount of time prior to September 27, 2007. We empirically evaluated this assumption in several ways. First, we explored whether there were any differences in the proportion of trials that were launched in each of the distinct clinical conditions shown in Supplementary Table 3 prior to 2007 or after 2008. We identified 3 conditions representing a significantly lower (at the $p<0.1$ level) proportion of the portfolio after 2008 versus prior to 2007: Hodgkin's lymphoma, leukemia, and esophageal cancers. However, the absolute differences were small and were likely spurious findings given the large number of statistical tests performed. Second, we explored whether the distribution of incidence of conditions being studied differed in trials launched before or after September 2007. Such a difference might occur if trials were more or less likely to register trials in rare conditions, for example, which could potentially bias our findings as our measure of competition is incidence-adjusted. However, we found a nearly identical distribution of incidence of conditions being studied before or after 2007 (Supplementary Figure 1).

We therefore assumed the portfolio of trials registered before September 2007 was representative of the proportion of trials started in each clinical condition over time. We recalibrated the total number of trials in each condition by multiplying the proportion of trials in each clinical condition by the ratio of observed to expected total trials (i.e. a Bayes factor), calculated quarterly. To incorporate uncertainty in this recalibration, we took 50 bootstrap samples with replacement of the entire dataset, calculated a Bayes adjusted measure of competition in each, and combined the estimation results using Rubin's rules when using stepwise selection strategies. When using LASSO, we calculated the mean coefficients from all MI estimations.

Sensitivity Analyses for Measure of Competition

We conducted several sensitivity analyses to assess the robustness of our results with respect to the recalibrated measure of competition. First, we explored the association between competition and poor accrual in a pre-specified subgroup of trials that started after September 27th, 2008 (one year after the requirement to register all new trials). There were 130 NCTN-sponsored trials in this analysis, 31 of which experienced poor accrual. Overall there was a

strong association between level of competition and poor accrual (OR per additional competing trial available per 10,000 eligible patients: 1.88 [95% CI: 1.18, 2.99]).

Second, we constructed a prediction model using only trials launched in 2000 to 2004 and evaluated whether including a measure of competition in our model improved discrimination of predictions made for trials started after 2008. Including competition in the model improved the AUC in the out of sample predictions from 0.692 to 0.714.

Third, we evaluated how our main results would have changed without including a measure of competition. If we omitted competition from the set of possible predictors, the remaining variables included in our final prediction model would not have changed. Furthermore, the AUC of the model on trials launched in 2000-2011 without competition was 0.71.

Lastly, we explored different ways to measure competition, specifically calculating the total number of trials opened within the previous two or three years of the index trial, or counting all trials that were open for enrollment at the time the index trial started. Overall our results were very similar across definitions, with the effects slightly attenuated when longer time frames were used, although with longer time frame the scales change as well. For example, the odds ratios were 1.30 (95% CI: 1.16, 1.47) and 1.03 (95% CI: 1.01, 1.04) for 2-year and 'all open' measures of competing trials.

As the goal of these analyses is prediction, we included the measure of competition that appeared to have the greatest predictive properties, which we evaluated in several ways. When all measures were included in the stepwise regression models, the measure of competition based on trials opened in the previous one year was consistently included in the final model, whereas none of the other measures of competition were included. Forcing the inclusion of additional measures of competition into the final model actually lowered the AUC very slightly.

Lastly, we conducted a sensitivity analysis using the LASSO to select predictors (described below). A key strength of the LASSO approach is the ability to handle correlated variables. Our different measures of competition are highly correlated. Selecting predictors using the LASSO selected the a measure of competition based on the total number of trials opened within the previous year, 2 years, and 3 years (but not all open trials); however, despite including these additional correlated predictors in the model, the overall predictive accuracy was not importantly improved. Therefore we felt that the measure of competition measured by the number of trials opened in the previous year provided the best predictive properties among the set considered.

Selecting Predictors According to the LASSO

The LASSO is a penalized multivariable logistic regression with a bound on the absolute magnitude of the regression coefficients. We selected the optimal shrinkage tuning parameter (lambda) using repeated 10-fold cross-validation. We explored inclusion of interaction terms by conducting the analyses in two stages: in the first stage we selected the important marginal predictors and the in the second we evaluated interactions between trial phase and the other supported predictors. Statistical analyses were conducted using the R statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria) with the *glmnet* package. The penalized coefficients for the prediction model selected using the LASSO are shown in Supplementary Table 7.

Supplementary Table 4. Beta Coefficients for Final Multivariable Logistic Regression Model of Predictors of <50% Accrual to NCTN-Sponsored Phase II and III Trials Registered in ClinicalTrials.gov and Started Between 2000 and 2011.

Risk Factor	Beta Coefficients
Number of competing trials per 10,000 eligible patients per year	0.63
Phase III (vs II)	0.62
Enrollment fraction (% of eligible population), per %	25.53
Enrollment fraction, spline 1	5487.44
Enrollment fraction, spline 2	-725.59
Targeted therapy	-0.57
Radiation therapy	0.59
Annual incidence of clinical condition(s), per 10,000	-0.01
Tissue sample required to assess eligibility	0.23
Investigational new drug	-1.07
Metastatic setting	0.38
Sample size, per 100	-0.05
More than one condition evaluated	0.68
Common solid tumor setting (prostate, breast, lung, colon)	0.84
Interaction term (Phase III x Investigational new drug)	0.90
Intercept	-3.10

We use a spline function with knots at 0.016% and 0.116% to model the non-linear relationship between enrollment fraction and low accrual. State code to generate the truncated power basis for the natural cubic spline (i.e. new variables for each interior knot): `spbase enroll_fraction, gen(enroll_fraction_sp) knots(0.0154, 0.1160)`

Supplementary Table 5. Beta Coefficients for Multivariable Logistic Regression Model of Predictors of <25% Target Accrual to NCTN-Sponsored Phase II and III Trials Registered in ClinicalTrials.gov and Started Between 2000 and 2011.

Risk Factor	Beta Coefficients
Number of competing trials per 10,000 eligible patients per year	0.47
Phase III (vs II)	1.14
Enrollment fraction (% of eligible population), per %	27.6
Enrollment fraction, spline 1	6029
Enrollment fraction, spline 2	-796
Radiation therapy	0.51
Investigational new drug	-0.62
Sample size, per 100	-0.04
More than one condition evaluated	0.60
Intercept	-3.54

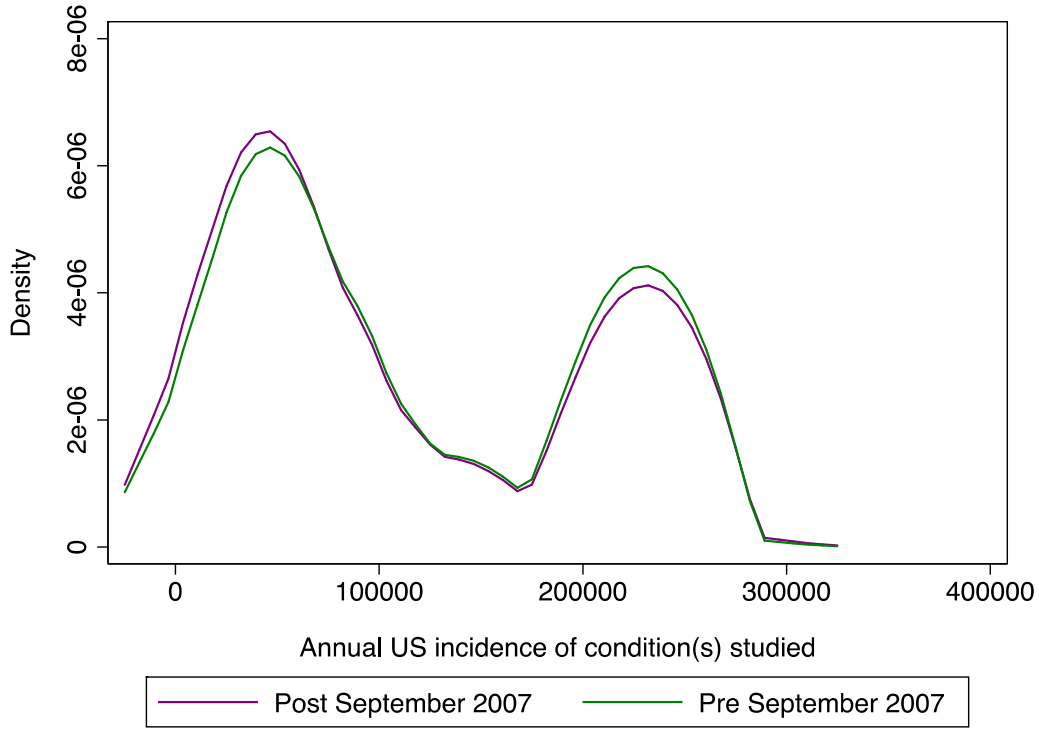
Supplementary Table 6. Beta Coefficients for Final Multivariable Logistic Regression Model of Predictors of ≤75% Accrual to NCTN-Sponsored Phase II and III Trials Registered in ClinicalTrials.gov and Started Between 2000 and 2011.

Risk Factor	Beta Coefficients
Number of competing trials per 10,000 eligible patients per year	0.55
Phase III (vs II)	0.67
Enrollment fraction (% of eligible population), per %	3.93
Enrollment fraction, spline 1	675.07
Enrollment fraction, spline 2	-88.92
Targeted therapy	-0.55
Surgery or procedure	-0.71
Radiation therapy	0.47
Annual incidence of clinical condition(s), per 10,000	-0.02
Tissue sample required to assess eligibility	0.42
Investigational new drug	-0.68
Metastatic setting	0.38
Sample size, per 100	-0.03
More than one condition evaluated	0.61
Common solid tumor setting (prostate, breast, lung, colon)	0.65
Intercept	-1.88

Supplementary Table 7. Sensitivity analysis: penalized beta coefficients for multivariable logistic regression model of low accrual where predictors were selected using the LASSO.

Risk Factor	Penalized Beta Coefficients
Number of competing trials opened in previous year per 10,000 eligible patients per year	0.48
Number of competing trials opened in previous 2 years per 10,000 eligible patients per year	0.10
Number of competing trials opened in previous 3 years per 10,000 eligible patients per year	-0.008
Phase III (vs II)	0.26
Enrollment fraction (% of eligible population), per %	0.92
Targeted therapy	-0.72
Radiation therapy	0.59
Multimodality	0.03
Surgical or procedural intervention	-0.39
Annual incidence of clinical condition(s), per 10,000	-0.03
Tissue sample required to assess eligibility	0.27
Investigational new drug	-1.02
Metastatic setting	0.01
Sample size, per 100	-0.04
More than one condition evaluated	0.42
Priority of fast track review	0.23
Common solid tumor setting (prostate, breast, lung, colon)	0.83
Interaction term (Phase III x radiation)	-0.008
Interaction term (Phase III x annual incidence, per 10,000)	0.016
Interaction term (Phase III x investigational new drug)	0.85
Interaction term (Phase III x metastatic setting)	0.74
Interaction term (Phase III x more than one condition evaluated)	0.52
Randomized design	0.34
Placebo control	-0.56
Intercept	-2.24

Supplementary Figure 1. Empirical distribution of phase II/III trials in cancer opened between 2000 and 2011 (n=10,084) by incidence of the condition(s) being studied.



Note: Distributions estimated using locally weighted scatterplot smoothing, separately for trials launched before and after September 2007. The density peak around 220,000 represents primarily trials in breast, prostate, and lung cancers.

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